THE BARKER HYPOTHESIS: HOW PEDIATRICANS WILL DIAGNOSE AND PREVENT COMMON ADULT-ONSET DISEASES

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Over a century ago William Osler wrote the *Principles and Practice of Medicine* (1). Not only did this become the definitive medical text of its day, but it also clearly defined, from the standpoint of medical education, the transition from the treatment of symptoms to the treatment of diseases based on pathophysiology. Now, a century later, with the emergence of the advances in human genetics a second book has been written, *Genetic Medicine: A logic of Disease* by Barton Childs (2). Two major messages from Childs' book are:

1) In the 21st Century medicine, will be directed toward treating individuals, not diseases.
2) Health will be defined as a function of gene-environmental homeostasis.

By far, one of the most pressing problems in American medicine is the understanding of the origins and the treatment of common complex adult-onset medical disorders as obesity, coronary artery disease, hypertension, and type II diabetes (metabolic syndrome). In this article I will examine the role of evolution as a major contributor to the origins of these common disorders. I will also explore how the origins of these disorders are explainable through gene-environment homeostasis.

THE ROLE OF EVOLUTION IN COMMON COMPLEX DISORDERS

"*Nothing in biology makes sense except in the light of evolution.*" Theodosius Dobzhansky 1964 (3).

For the sake of argument here, the theory of evolution has two major characteristics. First, our genome has evolved in a manner that assures sufficient variability in the genetic code and flexibility in the controls of gene expression so that the human species can readily

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adapt to changes in our environment. Our species has been successful because it has been able to adapt to dramatically differently environmental conditions. Second, the variety of adaptations that are made over evolutionary time are focused on two absolute necessities. First, the species must produce healthy individuals able to adapt as a developing fetus to the *in utero* environment and as an infant to the immediate postnatal environment (successful reproduction). Secondly, these children must grow old enough to also have children and to protect their young (propagation of the species). Taken together then evolution has over time led to a variable genome and the flexibility of the programming of genes to assure that the human species survives to thirty to forty years of age at most. Stated differently, our genetic code and the adaptations in the programming of genes are blind to any condition which limits the human species after the age of forty. Since the most common complex disorders listed above begin to show significant consequences in regards to health in the later, years one might propose that evolution of adult onset complex disorders are a byproduct of evolution which is essentially blind to the maladaptive consequences of older age (greater than 40 years). One might suppose then that these common adult onset diseases are the results of how multiple genes were turned off or on to optimize perinatal and early adult survival.

Modern genetics and genomics have now taught us that genetic variability between individuals goes beyond simple variations in the code itself. Sources of genetic variation between individuals can range from variance of a single base pair to large deletions or insertions which can be greater than two megabases (Table 1). Indeed, Redon et al. in a recent publication in *Nature* suggest that copy number variations (deletion, insertions, inversions, copy number variation and segmental duplication of genes) has been found in almost 1500 regions of the human

TABLE 1
Sources of Variation in the Genetic Code

■ Single nucleotide polymorphisms (SNPs) - ~1/1000 bp or at least 3 × 106	1 bp
■ Insertion/deletions	few bp
■ Short tandem repeats	few bp
■ Gene Copy number variation (CNVs)-Total of 1447 CNV regions covering 360 Mb (12% of the genome!!)	1 to 100s of kb
■ Cytogenetic deletions/insertions	>2 Mb
■ Aneuploidy	>100 Mb

SNP - single nucleotide polymorphisms.
CNV - copy number variations.

genome and may represent as much as 12% of the entire genome [4]. Flexibility in gene expression has been illustrated by the remarkable heterogeneity in the expression of genes in identical twins seen early in childhood, even when raised in the 'same' environment [5].

ORIGIN OF COMPLEX ADULT ONSET DISEASES (EPIGENETICS)

Perhaps the single most important observation made in the twentieth century related to the origins of complex adult onset disorders was made by Barker and his colleagues [6]. In studying coronary artery disease death rates among 100,000 men and women in Herpshirt, United Kingdom from 1911–1930, it became apparent that birth weight was inversely correlated with increased early death secondary to coronary heart disease. This inverse relationship between birth weight and coronary artery disease death rates has been reproduced in populations from all continents (except Africa) (Table 2). Several studies indicate that birth weight is not determined by genetic variation but by prenatal environment [7]. Furthermore, birth weight and rates of growth in the first two to three years of life (also heavily dependent on environment not genetic influences) have also been associated with adult onset hypertension and type II diabetes (Figure 1) [8]. It appears that adaptations to prenatal and postnatal environments establishes patterns of interaction between genes which control a variety of cellular and organ functions, which allows individuals to survive early prenatal and postnatal life but which have adverse consequences much later. Furthermore, adaptations made *in utero* to a hostile prenatal environment may place the infant at an adverse risk for adult onset diseases if the subsequent postnatal environment is not matched to that found in prenatal life.

TABLE 2
Confirmation of the Barker Hypothesis (inverse relationship of birth weight and Coronary artery disease)

Number of Subjects Studied	Classification of Subjects	Reference
70,297	Nurses in the U.S.	[17]
2,500	Men in South Wales	[18]
517	Men and Women in India	[19]
3,300	Men in Finland	[20]
15,000	Men and Women in Sweden	[21]
210,662	Danish men and women	[10]

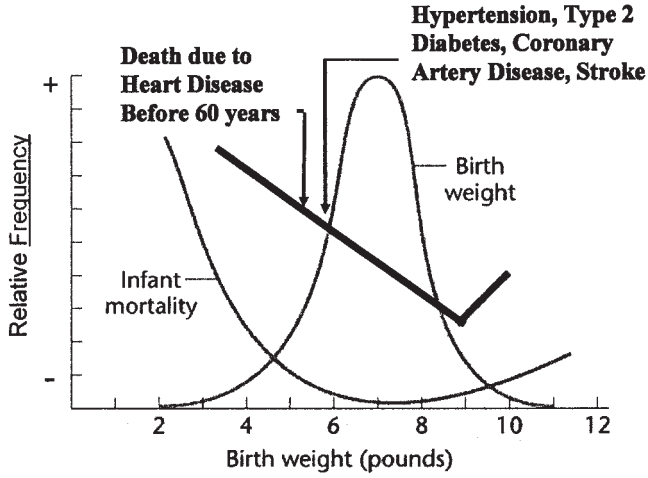

FIG. 1. Relation of birth weight to infant mortality and Complex Adult-Onset Disease.

Although adaptations to the environment which lead to low birth weight may ultimately result in adult onset hypertension, coronary artery disease and type II diabetes, higher birth weights also appear to have adverse consequences (Figure 2). Two large studies have now shown that in adults there is a 7% increase of cancer risk per 1,000

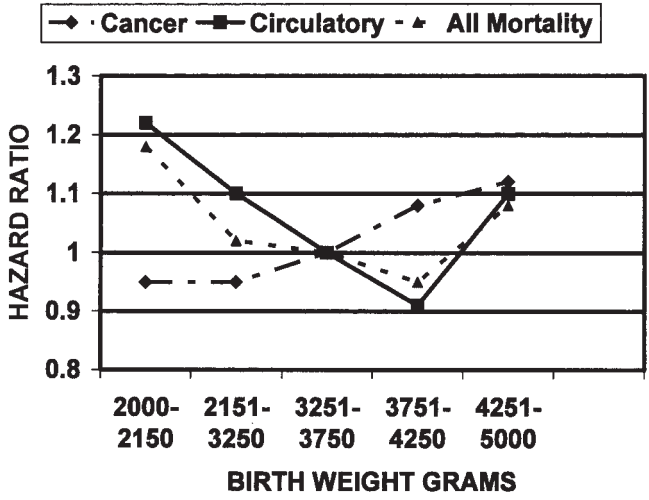

FIG. 2. Hazard ratio of birth weight in grams for cancer mortality (◆), circulatory disease mortality (■), and all cause mortality (▲) among 210,662 Danish men and women combined [10].

gram increase in birth weight over a two to five kilogram range in both males and females [9, 10]. Larger head circumference and length at birth, not simple birth weight, is also associated with a five fold increase risk of pre-menopausal breast cancer [11].

IATROGENIC CAUSES OF COMPLEX ADULT ONSET DISORDERS

Indeed, it may appear that physicians have contributed unwittingly to the onset of some adult onset diseases by attempting to feed newborn infants high caloric high protein diets in conditions in which it was perceived that accelerated weight gain was optimal weight gain. For example, Singhal et al [12] in a clinical trial performed in the late 1970's, randomized preterm infants to normal caloric diets or to a high protein high carbohydrate diet. After randomization the specific diets were administered for four weeks and stopped when the infants reached 2000 grams. After 4 weeks the infants were off study and allowed to eat whatever their parents wished (or doctors suggested). A twenty year follow up of these infants now shows that those given a high carbohydrate, high fat diet, indeed, have elevated pre-insulin levels. The differences seen in these pre-insulin levels are in the range that one uses to distinguish normal values from those of adults who will develop type II diabetes. Thus, relatively brief nutritional interventions in early infancy may have profound metabolic consequences in adults, predisposing to type II diabetes.

Intrauterine development can similarly have effects on development of more proximal childhood diseases. Brooks et al demonstrated in a cross sectional analysis of 8,071 children that birth weight was highly correlated inversely with the frequency of asthma diagnosed before the age of 3 [13]. Others have shown that prenatal environment may have effects on the onset in children of acute leukemia [14].

SUMMARY

Since the original observations of Barker, it has become apparent that environmental factors during prenatal and postnatal life can have profound effects on the programming of intracellular signals, cell-to-cell interactions, and metabolic pathways. These adaptations of the human genome can affect the onset of both adult and childhood disorders. One might imagine that perinatologists and pediatricians may be able to screen infants for increased risks to diseases by whole genome analysis, searching for variation in the genetic code, and searching the epigenome for variations in gene expression. Furthermore, observa-

tions exist in prior clinical trials [12] and in animal models [15, 16] that these same physicians may be able to alter certain programs thereby reducing risks to these disorders.

REFERENCES

1. Osler W. The principles and practice of medicine, designed for the use of practitioners and students of medicine. New York: D. Appleton and Company; 1892.
2. Childs B. Genetic medicine: a logic of disease. Baltimore: Johns Hopkins University Press; 1999.
3. Dobzhansky T. Biology, Molecular and Organismic. Am Zool 1964;4:443–52.
4. Redon R, Ishikawa S, Fitch KR, et al. Global variation in copy number in the human genome. Nature 2006;444:444–54.
5. Fraga MF, Ballestar E, Paz MF, et al. Epigenetic differences arise during the lifetime of monozygotic twins. Proc Natl Acad Sci U S A 2005;102:10604–9.
6. Barker DJ, Winter PD, Osmond C, Margetts B, Simmonds SJ. Weight in infancy and death from ischaemic heart disease. Lancet 1989;2:577–80.
7. Kramer MS. Determinants of low birth weight: methodological assessment and meta-analysis. Bull World Health Organ 1987;65:663–737.
8. Thompson JN. Fetal nutrition and adult hypertension, diabetes, obesity, and coronary artery disease. Neonatal Netw 2007;26:235–40.
9. Ahlgren M, Wohlfahrt J, Olsen LW, Sorensen TI, Melbye M. Birth weight and risk of cancer. Cancer 2007;110:412–9.
10. Baker JL, Olsen LW, Sorensen TI. Weight at birth and all-cause mortality in adulthood. Epidemiology 2008;19:197–203.
11. McCormack VA, dos Santos Silva I, De Stavola BL, Mohsen R, Leon DA, Lithell HO. Fetal growth and subsequent risk of breast cancer: results from long term follow up of Swedish cohort. Bmj 2003;326:248.
12. Singhal A, Fewtrell M, Cole TJ, Lucas A. Low nutrient intake and early growth for later insulin resistance in adolescents born preterm. Lancet 2003;361:1089–97.
13. Brooks AM, Byrd RS, Weitzman M, Auinger P, McBride JT. Impact of low birth weight on early childhood asthma in the United States. Arch Pediatr Adolesc Med 2001;155:401–6.
14. Gruhn B, Taub JW, Ge Y, et al. Prenatal origin of childhood acute lymphoblastic leukemia, association with birth weight and hyperdiploidy. Leukemia 2008; 22:1692–7.
15. Symonds ME, Gardner DS. Experimental evidence for early nutritional programming of later health in animals. Curr Opin Clin Nutr Metab Care 2006;9:278–83.
16. Brakefield PM, Gems D, Cowen T, et al. What are the effects of maternal and pre-adult environments on ageing in humans, and are there lessons from animal models? Mech Ageing Dev 2005;126:431–8.
17. Rich-Edwards JW, Stampfer MJ, Manson JE, et al. Birth weight and risk of cardiovascular disease in a cohort of women followed up since 1976. Bmj 1997;315:396–400.
18. Frankel S, Elwood P, Sweetnam P, Yarnell J, Smith GD. Birthweight, body-mass index in middle age, and incident coronary heart disease. Lancet 1996;348: 1478–80.
19. Stein CE, Fall CH, Kumaran K, Osmond C, Cox V, Barker DJ. Fetal growth and coronary heart disease in south India. Lancet 1996;348:1269–73.

20. Forsen T, Eriksson JG, Tuomilehto J, Teramo K, Osmond C, Barker DJ. Mother's weight in pregnancy and coronary heart disease in a cohort of Finnish men: follow up study. Bmj 1997;315:837–40.
21. Leon DA, Lithell HO, Vagero D, et al. Reduced fetal growth rate and increased risk of death from ischaemic heart disease: cohort study of 15 000 Swedish men and women born 1915– 29. Bmj 1998;317:241–5.

DISCUSSION

Mitch, Houston: Thank you, very intriguing. One sort of group of diseases that's been suggested as having genesis from this Barker hypothesis is kidney disease and specifically a reduced number of functioning nephrons leading to: A, hypertension and B, possibly ultimately to kidney disease per se. I was wondering on this last group of examples you showed us, was there anything done about kidney disease?

Dover, Baltimore: Yeah, in fact, this group of children actually was not looked at. You know what is very interesting about that is there are animal models now that will allow you to reproduce this and one of the most interesting animal models is a mouse which uniformly will become hypertensive, and if you manipulate the nutrition before those mice are born, you can make them become hypertensive much earlier and, in fact, there are biochemical markers, renin-angiotensin ratios and other things that actually, if you manipulate pharmacologically in the first weeks after those mice are born, you can completely reverse the effect, and so that programming model, as far as hypertension is concerned, is really one of the most exciting ideas, because it may say that, in fact, there may be approaches to how we might even reprogram, particularly in the first few weeks of life.

Griner, Boston: Thank you for your presentation. I wondered how the Barker hypothesis applies to multiple births, twins, triplets and so on. Are they still at the same risk, or is it the total birth weight?

Dover, Baltimore: Not enough data yet, except that most pediatricians and certainly obstetricians know that with twin births and multiple births there is usually a winner and a loser. That is, the weights can be very discrepant in the two and so the follow up data that I have seen, and it's not really enough yet to convince me, is that that child who actually was born smaller, and actually this is done in identical twins, actually seems to have more risk for cardiovascular disease as they grow older. So we don't know yet whether that data is complete, but there are certainly at least two studies that I am aware of that suggest the smaller of the identical twins actually may develop cardiovascular disease earlier.

Hay, Denver: That was nice, George. Just to reassure everybody, not all is as bad as you pointed out in the Singhal study from Alan Lucas' group. The same group of infants studied at 16 or so years of age - the group that got more food, the higher nutrient diet as premature babies—actually has a larger caudate volume and that directly correlates with intellectual development. So they may be smaller, and they may have a predisposition to diabetes and cardiovascular disease, but they are smarter, but at least that is the idea. So if any of you have some small children in your family, don't worry that much. Could you reflect on the cancer data that you showed us where the phenotype of the fat distribution because all IUGR babies tend to have more fat, but it is visceral, whereas the infant of the diabetic mother and the babies that you are seeing or purporting from these Danish studies and the other groups, have a larger body size would likely reflect subcutaneous fat?

Dover, Baltimore: Well, it is very interesting, and again, we talked about this

yesterday. I haven't been able to pull out any unifying hypothesis, but what is coming out of looking really at these infants, large and small, is: there are clearly differences in cytokine circulating stem cells, and in fact, responses in stem cells as far as cell division is concerned is based on some programming that had to happen in utero in the prior nine months. Now how that will fit in to distribution of adipose versus subcutaneous fat, how it might, in fact, have something to do with the predilection for stem cells to divide or to differentiate is a complete leap of faith after that, but you know there are windows of opportunity now to really begin to ask some of those questions.

Barondess, New York: George that was a spectacular talk. You have described one set of very important, early determinates of adult expression of chronic disease—not adult onset but adult expression. That is followed by a series across the life course of other epigenetic modifiers that also affect the risk of atherosclerosis, diabetes, metabolic syndrome and so on, so that what is required is a life course approach to this in the hands of basically all physicians to get at risk factors as they appear. What I want to ask you is how do you propose to get the pediatricians organized and mobilized to begin to act on, at least this first, very early set of important determinates, because once you tell us how you are going to get the pediatricians to behave in relation to this, then we can figure out what to do with the internists?

Dover, Baltimore: Well its very interesting, because I think it is not only the pediatricians, it's the obstetricians!

Barondess, New York: I thought you said the pediatrician was going to fix this?

Dover, Baltimore: Well the obstetrician is going to have to help us, probably. I think the remarkable thing is, already pediatricians are beginning to look at growth curves in very different ways. Pediatricians used to push weight gain, particularly in smaller children. We wanted them to go from the 20^{th} percentile up to the 50^{th} percentile, because there was a subliminal message that, in fact, what you wanted to do was, you wanted them to be more normal and, in fact, we are actually backing away from that now. So pediatricians now are not trying to push people to cross these growth lines, and in addition, we are watching BMI and accelerated growth in a very different way. So we, as yet, have not had an effect, but I think we have some of the tools, and so my job, like coming here and educating mostly internists, is to go around and talk to pediatrics and begin to start talking about these very important tools and how we need to change practice in relation to them. So that's just the first step. I hope there is going to be some sound biology. However, that is going to come out of this. That is actually going to give us much more powerful tools.

Chapman, Jackson: One of my questions was already answered and that is: is there a difference in distribution of the fat; but the second question is: is there a time period when you get hypertrophy of the fat cells versus division of fat cells and more fat cells that would be present later in life?

Dover, Baltimore: I don't know the answer to that question. I think the only information we seem to have is that accelerated growth seems to be associated with these changes. These risk factors are the changes that occur in the first two years of life. That seems to be the most powerful determinate. Now, if we can put that together with something someone else might know about fat cells, we might be able to answer the question. I just don't know.

Lippman, Miami: I enjoyed that greatly. We have a fair amount of data on the breast cancer question, and it is a bit discrepant. The point here is that in an animal model that we first developed, it's true that if the offspring of mice were of higher birthweight, the mice did have a greater risk of breast cancer, but it didn't matter after birth whether the pups were nursed on thin mothers and then given a thin diet for the rest of their life. There was nothing the mouse pediatrician could do to reverse the *in vitro* imprinted

phenotype on this, and data that we developed with the National Registry with Lena Clark basically substantiated that. So I think that some of this programming, while extraordinarily relevant, may be out of our hands once you are out of the womb.

Dover, Baltimore: I think there are two evolving groups of data. One is that there is clearly a group of events that occur *in utero* in a program that it really doesn't matter how you grow afterwards, and there are others that say that you can manipulate maybe in the first two years of life growth and affect other things such as cardiovascular disease but possibly not cancer. I have to mention that I was at a very exciting symposium about four weeks ago, and a lady named Diana Barrett from Boston actually showed some remarkable data that you can actually look at gene expression in the fetus from the peripheral blood of mothers, and she is beginning to look at gene expression overdevelopment; and she is seeing very remarkable differences in the babies that are born "normal" of above 3 kilos versus those that are around the 2 kilo-1.5 kilo range. So, I think the window for understanding these phenomena even *in utero* is going to be accessible, and that is why I was mentioning that, perhaps, we are going to have to get the obstetricians involved.

Mackowiak, Baltimore: George, thank you, very thought-provoking. My question has to do with cause versus effect. I would like you to comment on that. One of the things we have done since the time of Hippocrates, is we've focused on making high things low and low things high, and one would extrapolate from your presentation and conclude that if we could just get the birthweight up, we would correct the problem, but it may be that the problem is not the low birthweight but the predisposition to the atherosclerosis or the diabetes which is causing the low birthweight, and hence, we don't have the solution to the problem.

Dover, Baltimore: Yeah, and I think again a very common issue that is addressed here is we don't have the physiology. We don't have the pathways to this, and I think, what I hope you can do with this is: it opens your mind to thinking about when all these adult diseases may be occurring. It is clearly not just the genes you have. There clearly are environmental factors that are there and it may, in fact, turn out that the same factors that are giving you coronary artery disease later on may be both environmental or genetic and are actually acting and being programmed *in utero.* So it is not hard to believe that they are both the same. It is just when do you want to believe it starts and when would you rather treat it? When you have a hypertrophied heart when you are going into heart failure or when you may have, in fact, an opportunity to begin to program things much earlier. That's the pediatrician's view.